

How To Improve Patient Selection in Individuals With Lower Extremity Amputation Using a Bone-anchored Prosthesis

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Abstract

Background Many patients with a lower limb socket-suspended prosthesis experience socket-related problems, such as pain, chronic skin conditions, and mechanical problems, and as a result, health-related quality of life (HRQoL) is often negatively affected. A bone-anchored

prosthesis can overcome these problems and improve HRQoL, but these prostheses have potential downsides as well. A valid and reliable tool to assess potential candidates for surgery concerning a favorable risk-benefit ratio between potential complications related to bone-anchored prostheses and improvements in HRQoL is not available yet. Having this information may inform treating physicians and patients when deciding whether to pursue bone-anchored prostheses.

Questions/purpose In this study, we asked: (1) What is the difference in HRQoL at 6, 12, and 24 months among patients who underwent lower limb bone-anchored prosthesis treatment after using a socket-suspended prosthesis preoperatively? (2) What factors are associated with change in HRQoL 24 months after lower limb bone-anchored prosthesis treatment? (3) Which complications occurred within 24 months after lower limb bone-anchored prosthesis treatment? (4) What factors are associated with minor to severe complications within 24 months after lower limb bone-anchored prosthesis treatment?

Methods A total of 206 patients who underwent lower limb bone-anchored prosthesis treatment (femoral or tibial) at the Radboud University Medical Center between May 2014 and September 2020 were included in this study. Of those, 8% (17 of 206) were lost to follow-up at 24 months without meeting a study endpoint (not attending the clinic unrelated to the bone-anchored prosthesis, re-amputation), and another < 1% (1 of 206) died prior to 24 months, leaving 92% (189 of 206) of the original group who had a follow-up time of at least 24 months. The mean $\pm$ SD age was 54.3 ± 12.7 years, and 72% were men. Amputation levels included 64% (139 of 218) transfemoral amputation, 3% (7 of 218) knee exarticulation, 32% (70 of 218) transtibial amputation, 0.5% (1 of 218) foot amputation, and 0.5% (1 of 218) osseointegration implant after primary amputation. Causes of amputation included 52% (108 of

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206) trauma, 8% (17 of 206) oncology, 19% (38 of 206) dysvascular, 12% (25 of 206) infection, 1% (2 of 206) congenital, and 8% (16 of 206) other. Primary outcomes were generic HRQoL (Short-Form 36 health survey mental component summary [MCS] and physical component summary [PCS] scores), disease-specific HRQoL (Questionnaire for Persons with a Transfemoral Amputation global score), and complication occurrence (infection, implant complications such as loosening or breakage, stoma-related problems, periprosthetic fracture, and death). Multivariable multiple regression was used to develop association models. These models demonstrated which group of characteristics were associated with change in HRQoL at 24 months of follow-up and occurrence of complications within 24 months of follow-up. Assessments were carried out at baseline (preoperative while using a socket-suspended prosthesis) and after 6, 12, and 24 months of bone-anchored prosthesis use.

Results Generic HRQoL PCS score improved 25% (β 9 [95% confidence interval (CI) 7 to 11]) at 6 months and maintained that improvement at the 12-month (β 9 [95% CI 7 to 11]) and 24-month (β 8 [95% CI 7 to 10]) follow-up visit compared with baseline ($p < 0.001$). The generic HRQoL MCS score did not change compared with baseline. Disease-specific HRQoL improved 77% (β 30 [95% CI 25 to 34]), 85% (β 33 [95% CI 28 to 37]), and 72% (β 28 [95% CI 24 to 33]) at 6-month, 12-month, and 24-month follow-up, respectively, compared with baseline ($p < 0.001$). Patients with the following group of characteristics were more likely to experience a better physical generic HRQoL at 24 months of follow-up: younger patients with a lower physical generic HRQoL, and a traumatic cause of amputation combined with a lower activity level. Patients with the following group of characteristics were more likely to experience a better disease-specific HRQoL at 24 months of follow-up: dysvascular cause of amputation, lower prosthetic comfort combined with a lower activity level, and lower prosthetic comfort combined with a lower or higher activity level. In addition, patients with an average mobility level were more likely to experience less improvement in disease-specific HRQoL at 24 months of follow-up. Infections were the most common complications in the total cohort (116 events in 206 patients), of which the majority consisted of soft tissue infections (98% [114 of 116]). Bone infection did not occur. Septic implant loosening occurred in 1% (2 of 214) of total implants (3% [2 of 66] of tibial implants), both treated with transfemoral amputation. Younger and higher functioning patients had the lowest risk of minor complications within 24 months of follow-up. Women, older patients, patients with a lower activity level, and older patients with more time since amputation had the highest risk of minor complications within 24 months of follow-up.

Patients with a higher disease-specific HRQoL had the highest risk of moderate or severe complications within 24 months of follow-up.

Conclusion In agreement with earlier research, this study confirmed that generic HRQoL and disease-specific HRQoL improved after bone-anchored prosthesis use. Additionally, this study confirmed that bone-anchored prosthesis has a relatively low likelihood of severe complications but with a high occurrence of minor complications. These were often successfully treated with nonsurgical interventions. Patients who have a favorable risk-benefit ratio between improvements in HRQoL and potential treatment-related complications are most eligible for a bone-anchored prosthesis. These findings may be helpful to patients and treating physicians to aid in patient selection and to inform patients about potential short-term expectations of treatment.

Level of Evidence Level III, therapeutic study.

Introduction

In the United States, the estimated number of individuals with lower limb amputation in 2005 was 1.6 million. By 2050, this number is expected to reach 3.6 million [85]. Global rates of patients with a lower limb amputation who are using a socket-suspended prosthesis vary from 48% to 95% [21, 22, 27, 30, 68, 70-72]. In this population, 34% to 76% experience socket-related problems such as pain, chronic skin conditions, and mechanical problems (suspension and stability issues) [14, 19, 24, 31, 53, 55, 57, 76]. As a result, health-related quality of life (HRQoL) is often negatively affected [38, 46, 65, 66]. HRQoL is a generic assessment regarding the level of individual perception of physical, mental, and social health as well as the effect that disease and treatment have on daily life [15, 42, 60]. Besides the generic assessment HRQoL (generic HRQoL), a disease-specific assessment of HRQoL (disease-specific HRQoL) exists that is designed for a specific patient population. A way of overcoming aforementioned socket-related problems is by changing the fixation method of the artificial limb. This can be achieved by using an osseointegration implant, which is permanently attached to the residual bone, protrudes through the skin, and is connected to the artificial limb, resulting in a bone-anchored prosthesis [49]. Research has demonstrated that eliminating the socket and its related problems positively influences generic HRQoL and disease-specific HRQoL [3, 4, 7, 9, 12, 13, 31, 32, 35, 36, 41, 48, 69, 80]. However, this positive change is observed in heterogeneous populations rather than individuals.

As personalized care is increasingly important in healthcare, understanding which variables are linked to positive outcomes is paramount [44, 51]. To achieve this,

a decision tool is essential. However, development of a decision tool concerning changes in HRQoL and the occurrence of complications in patients with bone-anchored prostheses is lacking in the reports of others [10]. This study analyzed which variables were associated with positive and negative outcomes and was a first step toward development of a decision tool that assesses potential candidates for bone-anchored prosthesis treatment. Currently, patients are eligible for a bone-anchored prosthesis if they experience irreversible problems with the prosthetic socket (including skin problems, loosening, perspiration) causing reduced activity level, participation level, and/or quality of life [9, 26, 80].

In this study, we asked: (1) What is the difference in HRQoL at 6, 12, and 24 months among patients who underwent lower limb bone-anchored prosthesis treatment after using a socket-suspended prosthesis preoperatively? (2) What factors are associated with change in HRQoL 24 months after lower limb bone-anchored prosthesis treatment? (3) Which complications occurred within 24 months after lower limb bone-anchored prosthesis treatment? (4) What factors are associated with minor to severe complications within 24 months after lower limb bone-anchored prosthesis treatment?

Patients and Methods

Study Design and Setting

This follow-up study was drawn from a longitudinally maintained database with usual care data on patients included for bone-anchored prosthesis treatment in the Radboud University Medical Center, Nijmegen, the Netherlands [47]. Effectiveness and complication outcomes for a part of this cohort were published earlier [7, 9, 48, 58, 69]. We chose a 24-month follow-up time because both largest improvement in HRQoL and most treatment-related complications occur within 24 months after bone-anchored prosthesis treatment [9, 69]. Assessments were carried out at baseline (preoperative while using a socket-suspended prosthesis) and after 6, 12, and 24 months of bone-anchored prosthesis use. This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology Statement (STROBE) [82].

Participants

A total of 206 patients underwent lower limb bone-anchored prosthesis treatment (femoral or tibial) at the Radboud University Medical Center between May 2014 and September 2020 and were included for this study (Fig. 1). Of those, 8% (17 of 206) were lost to follow-up at 24 months

without meeting a study endpoint (not attending to the clinic unrelated to the bone-anchored prosthesis or re-amputation) and another < 1% (1 of 206) died prior to 24 months, leaving 92% (189 of 206) of the original group who had a follow-up of at least 24 months (Fig. 1). Patients were eligible for a bone-anchored prosthesis if they were adults with irreversible socket-related problems resulting in limited prosthetic use and a decreased disease-specific HRQoL [26, 47]. Exclusion criteria were: the presence of severe diabetes, local infection, dysplasia of the bony remnant with anatomic anomalies resulting in the inability to implant a device (tibia or femur), metabolic disorders, radiotherapy on the residual limb, chemotherapy within 3 months before bone-anchored prosthesis treatment, age younger than 18 years, bone deformity, use of immunosuppressive drugs, or inpatients with serious cognitive or psychiatric disorders [9, 80]. Radiologic imaging results of the femur or tibia using orthogonal conventional radiographs or CT scans were obtained according to institutional protocols, as were results of the calibrated total view of both lower limbs, followed by a physical examination and interview. Patients' eligibility to receive a bone-anchored prosthesis was assessed by an experienced and dedicated team of medical professionals, including a rehabilitation physician, surgeon, prosthetist, and physical therapist [26], using abovementioned information combined with the outcomes of the Questionnaire for Persons with a Transfemoral Amputation (Q-TFA) [33].

Descriptive Data

At baseline, data on gender, age, BMI (accounting for limb loss using the adjusted body weight) [63], amputation level, cause of amputation, as well as the interval between primary amputation and surgery were collected [50, 73]. Surgical details (single- or two-stage), implant characteristics (type, width, and length), and rehabilitation characteristics (duration and number of sessions) were retrospectively collected. The mean $\pm$ SD age was 54.3 ± 12.7 years, and 72% were men. Amputation levels included 64% (139 of 218) transfemoral amputation, 3% (7 of 218) knee exarticulation, 32% (70 of 218) transtibial amputation, 0.5% (1 of 218) foot amputation, and 0.5% (1 of 218) osseointegration implant after primary amputation. Causes of amputation included 52% (108 of 206) trauma, 8% (17 of 206) oncology, 19% (38 of 206) dysvascular (due to critical ischemia), 12% (25 of 206) infection, 1% (2 of 206) congenital, and 8% (16 of 206) other (Table 1).

Intervention

The operative procedure consisted of either a two- or single-stage procedure. Two-stage procedures were used as

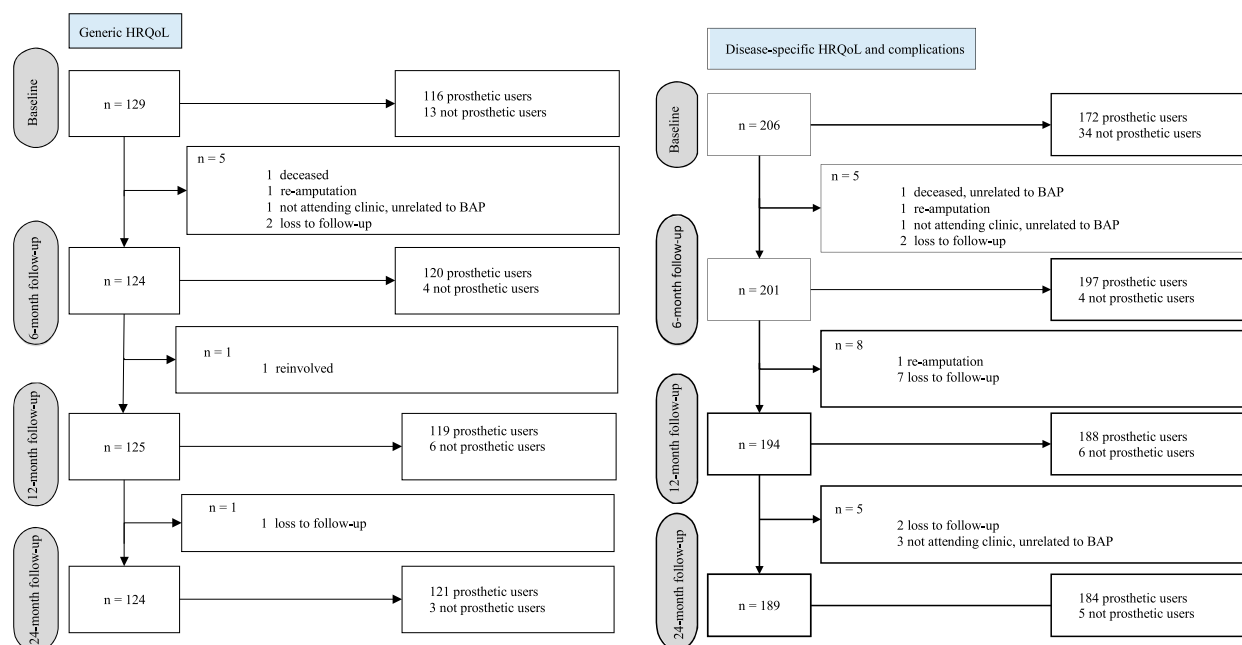


Fig. 1 This flow chart illustrates the number of patients in the study. One person missed the 6-month follow-up because of COVID-19 but participated in the 12-month and 24-month follow-up. BAP = bone-anchored prosthesis.

our standard approach; by contrast, in patients lacking sufficient soft tissue coverage for primary closure over the implant or logistic challenges (for example, patients from abroad), a single-stage procedure was performed with direct stoma creation. Steps undertaken during surgery included: shortening of the residual bone and removal of excess soft tissues, neuromas, or bone spurs when necessary; press-fit intramedullary insertion of the osseointegration implant; additional placement of transverse or lag screws in patients with transtibial or short transfemoral amputation; and creation of the circular skin opening (stoma), followed by mounting of the transcutaneous coupler (dual-cone adapter). All surgical steps were undertaken at once in single-stage procedures, whereas the stoma creation and dual-cone adapter mounting occurred approximately 6 to 8 weeks later in two-stage procedures. During the research period (2014 to 2020), three different implant systems were used: the Integral Leg Prosthesis (Orthodynamics GmbH or AQ Implants GmbH), the Osseointegration Prosthetic Limb (Permedica SPA), and the Bone Anchoring Device for Artificial Limbs (OTN Implants). The differences in implant types were a function of the fact that we treated three different types of conditions (short femur, long femur, and tibia). Also, a switch took place from CoCr implants to Ti implants during the time of our study. In addition, different manufacturers were used. This combination has resulted in seven types of implants (Supplemental Table 1; <http://links.lww.com/CORR/B374>). Implant designs followed the same overarching principle with differences related to amputation level.

These included (1) standard transfemoral amputation (minimum 160 mm in length from the lesser trochanter), (2) short transfemoral amputation (40 mm to 160 mm in length from the lesser trochanter), and (3) transtibial amputation (minimum 50 mm in length from the articular surface).

Rehabilitation started 1 week after a two-stage procedure and 3 weeks after a single-stage procedure. Rehabilitation comprised supervised group practices twice a week and was designed to increase hip abductor strength, decrease compensatory gait strategies, and increase the level of activity [49, 50]. The duration of rehabilitation was dependent on amputation level: 11 for transfemoral or 4 weeks for transtibial level. When necessary, a rehabilitation pause was inserted, mostly because of either a lack of hip abductor strength or pain. Rehabilitation was completed when patients achieved predefined individual goals [48, 50].

Study Outcomes

The primary study outcome was to analyze the difference in generic HRQoL and disease-specific HRQoL at 6, 12, and 24 months among patients who underwent a lower limb bone-anchored prosthesis after using a socket-suspended prosthesis preoperatively. Data collection on generic HRQoL started September 2017, and data collection on disease-specific HRQoL started May 2014. Consequently, the generic HRQoL cohort was smaller than

Table 1. Patient characteristics

Variable	Generic HRQoL cohort (n = 129)	Disease-specific HRQoL and complications cohort (n = 206)
Gender		
Men	77 (100)	72 (148)
Women	23 (29)	28 (58)
Age at inclusion in years	55 ± 12	54 ± 13
Time from amputation to baseline assessment in years	7 (3-23)	7 (3-23)
Baseline BMI ^a	29 ± 5	29 ± 4
Amputation		
Unilateral	95 (123)	94 (194)
Bilateral	5 (6)	6 (12)
Extremities treated ^b	135	214
Cause of amputation		
Trauma	57 (73)	52 (108)
Oncology	4 (6)	8 (17)
Dysvascular	15 (20)	19 (38)
Infection	12 (15)	12 (25)
Congenital	2 (2)	1 (2)
Other	10 (13)	8 (16)
Participants who did not use a prosthesis at baseline	10 (13)	18 (37)
Primary amputation level ^c		
Transfemoral amputation	59 (80 of 135)	64 (139 of 218)
Knee disarticulation	4 (5 of 135)	3 (7 of 218)
Transtibial amputation	35 (48 of 135)	32 (70 of 218)
Ankle disarticulation	1 (1 of 135)	1 (1 of 218)
Non-amputated (osseointegrated prosthesis at primary amputation)	1 (1 of 135)	1 (1 of 218)
Surgical details		
Single stage	26 (34)	19 (39)
Two stage	73 (94)	80 (166)
Primary amputation + implantation osseointegration in one stage	1 (1)	1 (1)
Rehabilitation duration in weeks ^d	11 (7-17)	13 (8-21)
Transfemoral amputation	13 (8-21)	15 (9-25)
Single stage		13 (8-17)
Two stage		15 (9- 27)
Transtibial amputation	9 (5-12)	9 (5-19)
Single stage		9 (6-19)
Two stage		9 (5-14)
Rehabilitation sessions		
Transfemoral amputation	20 (15-25)	20 (15-26)
Single stage		19 (14-22)
Two stage		19 (15-27)

Table 1. continued

Variable	Generic HRQoL cohort (n = 129)	Disease-specific HRQoL and complications cohort (n = 206)
Transfemoral amputation	9 (8-12)	10 (8-13)
Single stage		10 (8-17)
Two stage		10 (8-14)

Data presented as % (n), mean $\pm$ SD, or median (range).

^aBMI accounting for limb loss using adjusted body weight.

^bExtremities treated in the disease-specific HRQoL cohort (n = 135): in total, six patients with a bilateral osseointegration implant participated. Extremities treated in the generic HRQoL cohort (n = 214): in total, 12 patients with a bilateral amputation participated, of which eight had a bilateral osseointegration implant and four had a unilateral osseointegration implant.

^cPrimary amputation levels in the disease-specific HRQoL cohort: 135 extremities. Primary amputation levels in the generic HRQoL cohort: 218 extremities. Four participants had a bilateral transfemoral amputation, three participants had a bilateral amputation consisting of one transfemoral amputation and one transtibial amputation, and one participant had a bilateral amputation consisting of one transfemoral amputation and one knee exarticulation.

^dRehabilitation duration includes an optional rehabilitation pause.

the disease-specific HRQoL cohort (Fig. 1). Generic HRQoL was assessed using the Short-Form 36 health survey (SF-36), version 2 [1]. This questionnaire contains 36 questions about generic health in the month prior. A higher score reflects a superior health status. Two summary scores were used to assess physical and mental health: a physical component summary (PCS) score and a mental component summary (MCS) score. No minimum clinically importance difference has been defined for the SF-36 in patients with a lower limb amputation. Disease-specific HRQoL was assessed using the Q-TFA global score [33]. The global score (range 0 to 100) is a summary of three questions including perception of function, problems with the current prosthesis, and the perception of the current situation as a person with an amputation. Answers are given on a 5-point Likert scale. A higher score reflects a higher disease-specific HRQoL. Patients without a prosthesis, due to socket-related problems, only answered a single question concerning the current situation as a person with an amputation. This question contains five response alternatives: extremely poor, poor, average, good, or extremely good. In these patients, no continuous scale score was calculated. No minimum clinically important difference (MCID) has been defined for the Q-TFA. However, Hagberg et al. [33] reported a smallest detectable change of 19 points for the Q-TFA global score.

The secondary study outcome was to determine whether prosthetic use, walking ability, generic HRQoL, time since amputation, amputation level, age, cause of amputation, and prosthetic comfort before lower limb bone-anchored prosthesis treatment were associated with change in generic HRQoL at 24 months after lower limb bone-anchored prosthesis treatment. Additionally, we sought to determine whether prosthetic use, mobility level, walking ability, disease-specific HRQoL, time since amputation, amputation level, age, cause of amputation, BMI, gender, and prosthetic

comfort before lower limb bone-anchored prosthesis treatment were associated with change in disease-specific HRQoL at 24 months after lower limb bone-anchored prosthesis treatment. All factors were chosen based on previous publications [19, 23, 45, 56, 74] and clinical view of the authors (Appendix 1; <http://links.lww.com/CORR/B374>). Change in generic HRQoL and change in disease-specific HRQoL at 24 months were used as dependent variables in the association models. Potential factors associated with change in generic HRQoL and disease-specific HRQoL were analyzed in 124 and 172 participants, respectively. Baseline outcome values (level of function, activity, and satisfaction), patient characteristics, and demographics were used as independent variables in the association models.

Level of Function

Prosthetic use was assessed with the Q-TFA prosthetic use score and represented the patient-reported prosthesis wearing time (range 0 to 100), with a higher score reflecting a higher prosthetic use [33]. No MCID has been defined for the Q-TFA. However, Hagberg et al. [33] reported a smallest detectable change of 12 points for the Q-TFA prosthetic use score.

Level of Activity

Walking ability was assessed with the 6-minute walking test using a 10-meter course, recording walking distance in meters [52, 77]. No MCID has been defined for this test for individuals with a lower limb amputation. Mobility level was assessed using the Medicare Functional Classification Level, also known as the K-level, which consists of five

ordered categories: mobility K-level 0 (K0; a nonambulatory patient), mobility K-level 1 (K1; a patient with the ability to use a prosthesis for transfers or walking on even surfaces), mobility K-level 2 (K2; a patient who has the ability to walk with a prosthesis and can navigate low-level environmental barriers), mobility K-level 3 (K3; a patient with the ability to walk using a prosthesis in a variable cadence on different types of surfaces), and mobility K-level 4 (K4; a highly active patient using a prosthesis) [16]. No MCID has been defined for the mobility K-levels.

Level of Satisfaction

To assess prosthetic comfort, we used the prosthesis comfort score [50]. This score is a modification of the Socket Comfort Score [37]. Patients answered a single question, “How satisfied are you with your current prosthesis on a scale of 0 to 10?,” with the scale ranging from 0 (“not satisfied at all”) to 10 (“extremely satisfied”). No MCID has been defined for this score.

The third study outcome was to analyze complications occurring within 24 months after lower limb bone-anchored prosthesis treatment. Complication data were retrospectively extracted from medical records and the institutional registry. The treating surgeon contacted patients at standard follow-up points to assess the occurrence of potential complications. Patients contacted the treating surgeon or general practitioner in the event that a complication occurred between follow-up points. Complications assessed were: infection, implant failure (aseptic loosening or failure of osseointegration, intramedullary device breakage), stoma-related problems (hypergranulation/ke-loid formation and stoma-redundant tissue), periprosthetic fracture, and death [8]. Dual-cone adapter breakages were categorized as a complication of the external prosthetic components and were thus outside the scope of this study. Infections were classified as described by Al Muderis et al. [2] as follows: (1) low-grade soft tissue infection, (2) high-grade soft tissue infection, (3) bone infection, and (4) septic implant failure. Complications occurring between surgical stages, such as surgical site infections when there was two-stage surgery, were also recorded separately and described [29]. Complications were classified as minor or moderate/severe [8, 48] (Supplemental Table 2; <http://links.lww.com/CORR/B374>).

The fourth outcome was to determine whether mobility level, gender, age, BMI, cause of amputation, amputation level, time since amputation, single- or two-stage surgery, generic HRQoL, and disease-specific HRQoL before lower limb bone-anchored prosthesis treatment were associated with minor or moderate/severe complications within 24 months after lower limb bone-anchored prosthesis treatment. All factors were chosen based on previous

publications [11, 58] and clinical view of the authors (Appendix 1; <http://links.lww.com/CORR/B374>). The number of complications occurring within 24 months (including complications between surgical stages) was used as a dependent variable in the association models. Baseline outcome values, patient characteristics, and demographics were used as independent variables in the association models. Potential factors associated with complications were analyzed in 206 participants.

Ethical Approval

Ethical approval for this study was obtained from Radboud University Medical Center, Nijmegen, the Netherlands (number 2018-4962).

Statistical Analysis

Categorical data are presented as percentages and exact numbers and were calculated for various levels. Means $\pm$ SDs were calculated for normally distributed continuous variables. For nonparametric data, the median (range 25th percentile to 75th percentile) is presented. Normality was analyzed using a histogram and a Q-Q plot. First, mean change over time in generic HRQoL (SF-36 PCS and MCS scores) and disease-specific HRQoL (Q-TFA global score) compared with baseline was analyzed using generalized estimating equations for repeated measurements. All patients with a completed questionnaire at baseline were included in this available analysis. Mean change (β) is presented with 95% confidence intervals (CIs). For the Q-TFA global score, answers to the single question on the patients' overall situation as a person with an amputation at each time point are presented as descriptive statistics. Second, if there were significant differences, association models for change in generic HRQoL and disease-specific HRQoL between 24-month follow-up and baseline were developed. Third, complications data are presented on a patient and event level as descriptive statistics and stratified by osseointegration implant type (Supplemental Table 1; <http://links.lww.com/CORR/B374>). Fourth, two association models for both minor and moderate/severe complications occurring within 24 months after lower limb bone-anchored prosthesis treatment were developed using multivariable multiple regression. For all association models, multivariable multiple regression was used, and assumptions were tested and satisfied prior to proceeding. This complete case analysis excluded patients with missing values at baseline or 24 months of follow-up and, in the case of disease-specific HRQoL, also excluded patients who did not have a prosthesis. When there were missing data regarding the multivariable multiple regression

analysis, patient-wise deletion was used. In this study, no imputation methods were used. The rule of thumb was used to determine the number of factors per model: for every 10 patients, one factor was added [20, 64, 83]. Interaction effects were checked using a correlation matrix. If variables correlated significantly (Pearson correlation < 0.05), interaction effects were added to the multivariable multiple regression model [39]. Independent variables, with a p value < 0.1 , were entered in a backward elimination regression model with change in generic HRQoL, change in disease-specific HRQoL, and number of complications as dependent variables [79]. The adjusted percentage of explained variance (adjusted R^2) and standard error were used to examine model performance. SPSS, version 25 (IBM), was used for the generalized estimating equations analysis, multivariable multiple regression analysis, and to analyze complications. Stata, version 16 (StataCorp), was used to convert raw SF-36 PCS and MCS scores into norm scores. A more detailed description of the statistical analyses is available (Appendix 2; <http://links.lww.com/CORR/B374>).

Results

Differences in HRQoL at 6, 12, and 24 Months

Physical generic HRQoL and disease-specific HRQoL after lower limb bone-anchored prosthesis treatment improved at all time points compared with using a socket-suspended prosthesis before treatment. There was also an improvement over time in the overall situation as a person with an amputation compared with using a socket-suspended prosthesis. Mental generic HRQoL did not change over time. The SF-36 PCS score improved 25% (β 9 [95% CI 7 to 11]) at 6 months and maintained that improvement at 12 months (β 9 [95% CI 7 to 11]) and 24 months (β 8 [95% CI 7 to 10]) of follow-up compared with baseline ($p < 0.001$) (Fig. 2). The SF-36 MCS score did not change compared with baseline. The Q-TFA global score improved at all time points compared with baseline (Fig. 3). Improvements in the Q-TFA global score of 77% (β 30 [95% CI 25 to 34]), 85% (β 33 [95% CI 28 to 37]), and 72% (β 28 [95% CI 24 to 33]; $p < 0.001$) were found at the 6-month, 12-month, and 24-month follow-up visits, respectively. The overall situation as a person with a lower extremity amputation at each time point improved compared with baseline (Fig. 4). At baseline, 30% (62 of 206) of the patients scored their overall situation as a person with an amputation “poor” or “extremely poor.” Four percent (9 of 201) at 6 months, 5% (10 of 194) at 12 months, and 6% (12 of 189) at 24 months of all patients scored their situation as “poor” or “extremely poor.”

Factors Associated With Changes in HRQoL at 24 months

Younger patients, patients with a lower physical generic HRQoL, and patients who have low activity levels with a traumatic cause of amputation were more likely to experience a better physical generic HRQoL at 24 months after bone-anchored prosthesis treatment. Results of the analysis of generic HRQoL PCS score showed that younger age, lower generic HRQoL, and lower 6-minute walking test results combined with trauma as cause of amputation had a greater improvement in physical generic HRQoL between baseline and 24-month follow-up (Supplemental Table 3; <http://links.lww.com/CORR/B374>). This association model explains 42% of the variance of the change in the study population (Appendix 3; <http://links.lww.com/CORR/B374>).

Patients with a dysvascular cause of amputation, lower prosthetic comfort combined with a lower activity level, and lower prosthetic comfort combined with a lower or higher activity level were more likely to experience a better disease-specific HRQoL at 24 months after bone-anchored prosthesis treatment. In addition, patients with an average mobility level were more likely to experience less improvement in disease-specific HRQoL at 24 months after bone-anchored prosthesis treatment. Results of the analysis of disease-specific HRQoL showed that dysvascular cause of amputation, lower prosthetic comfort combined with lower 6-minute walking test results, as well as lower prosthetic comfort combined with mobility level K1 (low) or K4 (high) showed greater improvement in disease-specific HRQoL between baseline and 24-month follow-up. In addition, mobility level K2 (average) and K3 (average) had an association with less change in disease-specific HRQoL between baseline and 24-month follow-up (Supplemental Table 4; <http://links.lww.com/CORR/B374>). This association model explains 77% of the variance of change in the study population (Appendix 3; <http://links.lww.com/CORR/B374>).

Complications Within 24 Months

Infections were the most common complications in the total cohort (116 events in 206 patients), most of which consisted of soft tissue infections (98% [114 of 116]) (Table 2). Soft tissue infections were successfully treated with local measures or oral antibiotics in 86% (98 of 114) of patients. We observed no bone infections. Two patients with tibial implants developed septic implant loosening (1% [2 of 214] of total implants, 3% [2 of 66] of tibial implants); one patient underwent primary transtibial amputation as a result of posttraumatic osteomyelitis treated with an external fixator with pins at the level of the tibia and the other underwent transtibial amputation as a result of

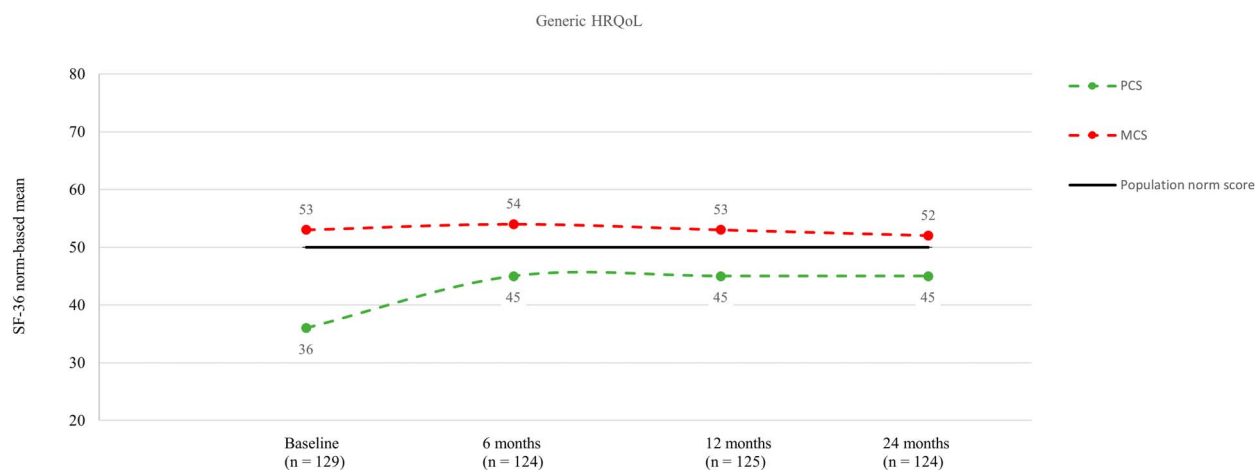


Fig. 2 This graph shows generic HRQoL at each time point. The red line reflects the SF-36 MCS score over time, the green line reflects the SF-36 PCS score over time, and the black line reflects the SF-36 population norm score over time. The SF-36 PCS score and MCS score are normalized to the general population (mean $\pm$ SD 50 $\pm$ 10). The SF-36 PCS scores over time were: baseline (T0) β 36; 6 months (T1) β 45; 12 months (T2) β 45; and 24 months (T3) β 45. Mean changes over time were T1 to T0 β 9 (95% CI 7 to 11)*; T2 to T0 β 9 (95% CI 7 to 11)*; and T3 to T0 β 8 (95% CI 7 to 10)*. The SF-36 MCS scores over time were: baseline (T0) β 53; 6 months (T1) β 54; 12 months (T2) β 53; and 24 months (T3) β 52. Mean changes over time were: T1 to T0 β 0 (95% CI -2 to 2); T2 to T0 β 0 (95% CI -1 to 2); and T3 to T0 β -1 (95% CI -3 to 1). *Zero is not contained within the 95% CI; change over time was statically significant. A color image accompanies the online version of this article.

diabetic Charcot arthropathy of the foot. The patient with the history of external fixator treatment underwent implant removal with debridement; intraoperative cultures grew *Candida albicans*. This patient experienced symptoms in the knee and chose not to be treated with prolonged

antibiotics or fungal medication; thus, a transfemoral amputation followed by femoral bone-anchored prosthesis treatment was successfully performed. The other individual was treated with a transfemoral amputation and died 8 months after amputation due to a myocardial

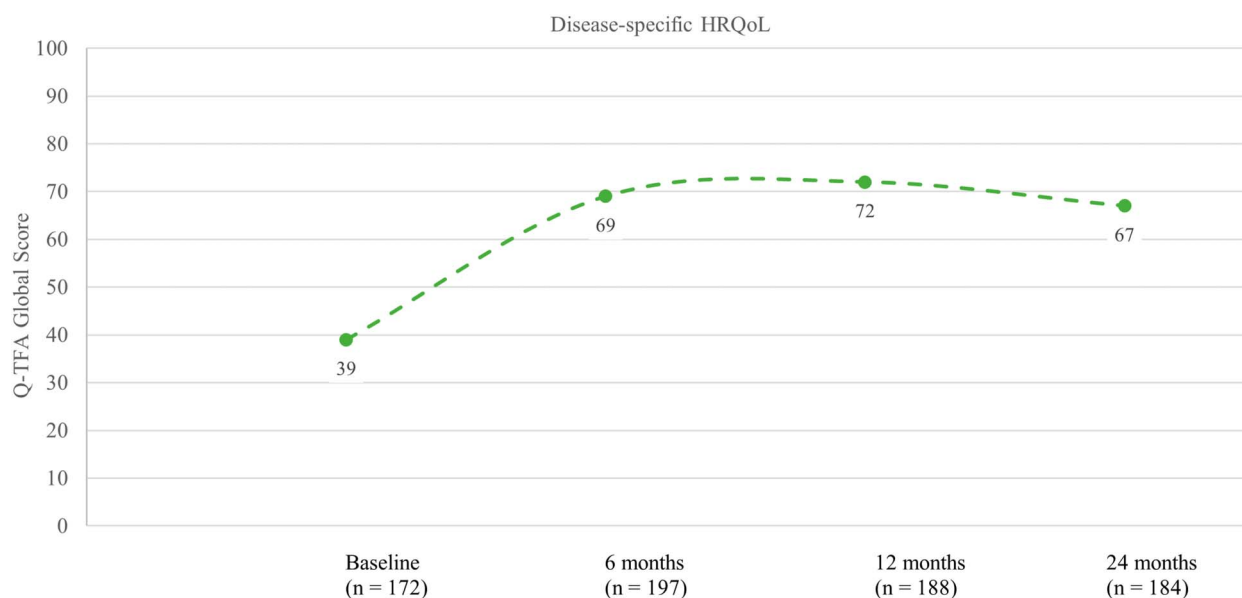


Fig. 3 This graph shows disease-specific HRQoL at each time point. The Q-TFA global scores (range 0 to 100) over time were: baseline (T0) 39; 6 months (T1) 69; 12 months (T2) 72; and 24 months (T3) 67. Mean changes over time were: T1 to T0 β 30 (95% CI 25 to 34)*; T2 to T0 β 33 (95% CI 28 to 37)*; and T3 to T0 β 28 (95% CI 24 to 33)*. *Zero is not contained within the 95% CI; change over time was statically significant.

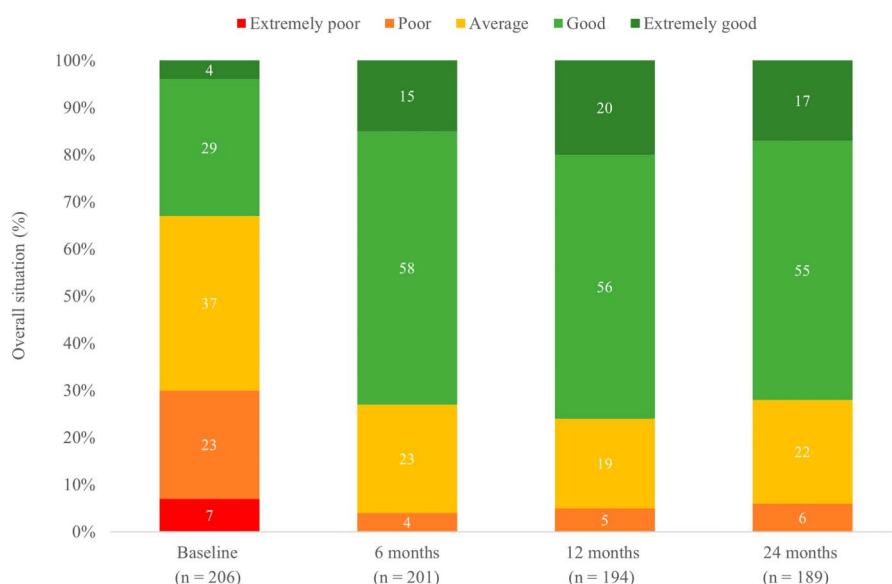


Fig. 4 This graph shows responses to the single question on overall situation at each time point for patients who have undergone amputation. Missing values: T0 (n = 0), T1 (n = 5), T2 (n = 12), T3 (n = 17). A color image accompanies the online version of this article.

infarction. No other deaths occurred. Stoma-related complications such as hypergranulation/keloid formation and soft tissue redundancy did not occur in patients with a tibial bone-anchored prosthesis, whereas those with a short femoral bone-anchored prosthesis experienced the highest incidence (15% to 27%) (Table 2). The occurrence of redundancy of soft tissues of the residual limb, resulting in stoma soft tissue irritation while mobilizing, was most often treated with surgery (68% [13 of 19] of events), whereas hypergranulation/keloid formation was most frequently treated with local measures (67% [18 of 27] of events). Aseptic loosening occurred in one individual with a standard femoral implant, which involved a radiologic diagnosis of partial distal loosening, and showed no signs of progression over time, with the patient experiencing no symptoms. Periprosthetic fractures only occurred in patients treated with standard femoral bone-anchored prosthesis, all of which occurred after falls (8% [9 of 119] events). Four fractures were treated conservatively (three were nondisplaced and one was an isolated major trochanteric fracture), and five fractures were treated by open reduction and internal fixation (two with a dynamic hip screw, two with cannulated screws, and one with a proximal femoral plate). None of these patients had loss of implant fixation. No intramedullary stem breakage occurred. Complications between surgical steps 1 and 2 occurred in 19% (32 of 170) of patients treated with two-stage surgery (Table 2). Most of these complications were surgical site infections (91% [32 of 35]) treated by surgical means (57% [20 of 35]), typically bringing step 2 of the

surgery forward in time to allow for debridement (80% [16 of 20] of surgically treated events). Two percent (3 of 170) of patients experienced noninfectious complications, all of whom were treated surgically (one patient had a post-operative hemorrhage and two patients had skin necrosis overlying the implant treated with premature stoma creation).

Factors Associated With Minor to Severe Complications

Younger patients with a higher activity level and patients with a traumatic cause of amputation combined with a higher activity level had the lowest risk of minor complications within 24 months after lower limb bone-anchored prosthesis treatment, while woman, older patients with more time since amputation, and patients with a lower activity level had the highest risk of minor complications within 24 months after lower limb bone-anchored prosthesis treatment. Results of the analysis showed that younger age in combination with mobility K-level 4 (high) and a traumatic cause of amputation in combination with mobility K-level 4 (high) had an association with the decreased occurrence of minor complications between osseointegration implant surgery and 24 months of follow-up. Additionally, women, older age, mobility K-levels 0 to 3 (low/average), and older age in combination with more time since amputation had an association with the increased occurrence of minor complications between osseointegration implant surgery and

Table 2. Complications

	Transfemoral (n = 119 patients; 122 implants)		Transtibial (n = 61 patients; 66 implants)		Short-transfemoral (n = 26 patients; 27 implants)		
Complication	Patients	Number of complications	Patients	Number of complications	Patients	Number of complications	Severity
Section 3a: Procedure-related complications and treatment							
Implant-related infection	36 (43)	65	44 (27)	43	19 (5)	8	
Low-grade soft tissue infection	24 (28) ^a	39	30 (18)	22	8 (2)	2	
Treatment							
Local measures	6 (7)	7	7 (4)	4			Minor
Oral antibiotics	18 (22) ^a	32	25 (15)	17	8 (2)	2	Minor
Parenteral antibiotics			2 (1)	1			Minor
Surgical treatment							Moderate
High-grade soft tissue infection	19 (23)	26	23 (14)	19	15 (4)	6	
Treatment							
Local measures	1 (1)	1			4 (1)	1	Minor
Oral antibiotics	13 (15)	18	20 (12)	13	4 (1)	1	Minor
Parenteral antibiotics	3 (4)	4	3 (2)	2			Minor
Surgical treatment	3 (3)	3	5 (3)	3	8 (2)	3	Moderate
Bone infection							
Septic implant loosening			3 (2)	2			
Treatment							
Explantation of the implant			3 (2)	2			Severe
Aseptic loosening	1 (1)	1					
Treatment							
Nonoperative treatment	1 (1)	1					Minor
Surgical treatment							Severe
Intramedullary stem breakage							Moderate
Hypergranulation/keloid	13 (16)	20			27 (5)	7	
Treatment							
Local measures	11 (13)	14			15 (4)	4	Minor
Sleeve placement	2 (2)	2			12 (3)	3	Moderate
Soft tissue surgery	3 (4)	4					Moderate
Stoma redundant tissue	9 (11)	12			15 (4)	6	
Treatment							

Table 2. continued

Complication	Transfemoral (n = 119 patients; 122 implants)		Transtibial (n = 61 patients; 66 implants)		Short-transfemoral (n = 26 patients; 27 implants)		Severity
	Patients	Number of complications	Patients	Number of complications	Patients	Number of complications	
Local measures	1 (1)	1			8 (2)	2	Minor
Sleeve placement	2 (2)	2			4 (1)	1	Moderate
Soft tissue surgery	8 (9)	10			12 (3)	3	Moderate
Extramedullary implant removal							Moderate
Periprosthetic fracture	8 (9)	9					
Treatment							
Conservative treatment	3 (4)	4					Moderate
Surgical treatment	4 (5)	5					Severe
Section 3b: Complications between surgical steps 1 and 2 ^b							
Total	20 (22)	24	10 (4)	4	23 (5)	5	
Surgical site infections							
Treatment							
Local measures							Minor
Antibiotics	8 (9)	10	3 (1)	1	5 (1)	1	Minor
Surgical treatment	10 (11)	12	5 (2)	2	18 (4)	4	Moderate
Other	2 (2)	2	3 (1)	1			Moderate

Data presented as % (n). The severity of complications has been defined (Supplemental Table 2; <http://links.lww.com/CORR/B374>). Bone infection (Grade 3) did not occur.

^aOne person had a bilateral amputation with a complication in both implants.

^bTransfemoral (n = 109; 111 implants); transtibial (n = 39; 41 implants); short-transfemoral (n = 22; 22 implants).

24 months of follow-up (Supplemental Table 5; <http://links.lww.com/CORR/B374>). This association model explains 46% of the variance of the occurrence of minor complications in the study population (Appendix 3; <http://links.lww.com/CORR/B374>).

Patients with a higher disease-specific HRQoL had the highest risk of moderate/severe complications within 24 months after bone-anchored prosthesis treatment. Results of the analysis showed that a higher disease-specific HRQoL had an association with the occurrence of moderate/severe complications between osseointegration implant surgery and 24 months of follow-up. This association model explains 19% of the variance in the occurrence of moderate/severe complications in the study population (Appendix 3; <http://links.lww.com/CORR/B374>).

Discussion

A bone-anchored prosthesis can overcome socket-related problems and improve HRQoL; however, these prostheses have potential downsides as well. As treatment with bone-anchored prostheses gradually evolves from the pioneer phase to standard care in high-prevalence countries (Australia, Germany, Sweden, the Netherlands), there is increasing necessity for predictable outcomes in terms of function, satisfaction, generic and disease-specific HRQoL, and complication risks. This study analyzed which variables are associated with positive and negative outcomes and is a first step toward the development of a decision tool that assesses potential candidates for bone-anchored prosthesis treatment. The current study showed

that physical generic HRQoL and disease-specific HRQoL after bone-anchored prosthesis treatment improved at all time points compared with using a socket-suspended prosthesis; there was also an improvement over time in the overall situation as a person with an amputation compared with using a socket-suspended prosthesis. Mental generic HRQoL, however, did not change. We determined which characteristics measured before bone-anchored prosthesis treatment were associated with change in HRQoL 24 months after bone-anchored prosthesis treatment. The current study demonstrated that major complications are uncommon after bone-anchored prosthesis treatment at 24 months of follow-up. Having this information may inform treating physicians and patients when deciding whether to pursue lower limb bone-anchored prostheses.

Limitations

Limitations of this study include selection bias as we only included patients for bone-anchored prosthesis treatment if the inclusion criteria were met. If our current criteria were accurate, the entire study population included patients with a potentially favorable ratio between potential complications associated with bone-anchored prosthesis treatment and potential improvement in HRQoL. This bias could cause an overestimation of the explained variance in the association model. Because we likely included the most favorable group using the current inclusion criteria combined with our clinical experience and “gut feeling,” there may be a small distribution in the outcome data resulting in a larger adjusted R^2 than was actually present [61]. The study of van den Bruel et al. [81] showed that a physicians’ first impression (gut feeling) when confronted with a clinical decision can often be more accurate than later analysis.

A limitation of the Q-TFA is that the global score cannot be reported in patients not using a prosthesis. Consequently, these patients were excluded from analysis regarding the first study question. The “overall situation as a person with an amputation” analysis contained both patients who did not use a prosthesis and patients who did use a prosthesis. By adding this analysis, we presented a more complete overview of the population. Consequently, disease-specific HRQoL probably improved less than when patients who did not use a prosthesis were included. We expected that patients who did not use a socket-suspended prosthesis because of socket-related problems would experience the greatest improvement in disease-specific HRQoL simply because they had the most potential for improvement (going from a person who did not use a prosthesis to one who walks with a prosthesis). In our study, 82% of patients were using a socket-suspended

prosthesis; therefore, improvement in disease-specific HRQoL was probably underestimated.

Association models developed in this study are not easily generalizable to other clinics. Therefore, it is important to carry out step 2 and step 3 of the process in developing a clinical decision tool; step 2 will validate the association model in a new clinical setting resulting in a prediction model and step 3 will evaluate this rule [54].

Mobility K-levels and the Q-TFA prosthetic use score were used to reflect activity level. However, mobility K-levels do not report the patients’ activity level but are used for choosing prosthetic components based on individuals’ need. Nevertheless, mobility K-levels in combination with the Q-TFA prosthetic use score provide a broad overview of the patient’s activity level. In addition, mobility K-levels are regularly used as a measure of activity in amputation research [17].

Difference in HRQoL at 6, 12, and 24 Months

Physical generic HRQoL and disease-specific HRQoL after treatment improved at all time points compared with using a socket-suspended prosthesis before treatment; there was also an improvement over time in the overall situation as a person with an amputation compared with using a socket-suspended prosthesis. Mental generic HRQoL did not change over time. Our findings are consistent with previously reported outcomes assessing HRQoL in patients with a bone-anchored prosthesis [3, 4, 7, 9, 12, 13, 31, 32, 34-36, 41, 48, 59, 69, 80]. Most of the aforementioned studies also reported on the overall situation as a person with an amputation. All reported an improvement when comparing the results to using a socket-suspended prosthesis, which is in accordance with our study [7, 9, 12, 13, 31, 32, 34-36, 48]. Nevertheless, a flattening and even decrease of the generic HRQoL curve (Fig. 2) and disease-specific HRQoL curve (Fig. 3) was observed between 12 and 24 months. We believe that this was the result of patients achieving a sense of normality with regard to the improvements in function after bone-anchored prosthesis treatment. The mental generic HRQoL over time in our study population was 0.2 to 0.4 SDs higher than that of the American population norm score, although this is not a clinically relevant difference. This may be attributed to cultural influence on generic HRQoL [43, 84]. Even though an MCID has not been defined for the SF-36 in patients with a lower limb amputation, a 0.5 SD change in mental and physical generic HRQoL is frequently described as clinically meaningful in populations with comparable health conditions (such as, orthopaedic oncology and rheumatoid arthritis) [62, 67, 75]. Consequently, regarding physical generic HRQoL, a clinically relevant difference was observed in our study population with

a difference of 0.9 SD. Regarding disease-specific HRQoL, we found an increase of ≥ 28 points in the disease-specific HRQoL at each time point compared with baseline. Hagberg et al. [33] reported a smallest detectable change of 19 points in the Q-TFA global score (disease-specific HRQoL). Therefore, we concluded that the increase in disease-specific HRQoL in our study was not a measurement error and may be considered clinically relevant.

Factors Associated With Change in HRQoL at 24 Months

The model for generic HRQoL explained 42% of the variance in change in generic HRQoL in the study population. Younger patients, patients with a lower physical generic HRQoL, and patients with low activity levels with a traumatic cause of amputation were more likely to experience a better physical generic HRQoL. These findings might be explained by the fact that younger patients with a lower level of function and subsequently a lower generic HRQoL using a socket-suspended prosthesis are no longer limited by the prosthetic socket, which consequently improves function and generic HRQoL. Subsequently, patients presenting with lower baseline generic HRQoL scores have the highest room for improvement. This may be the phenomenon often observed in cohort studies known as “progression to the mean.” Conversely, patients presenting with higher baseline scores have little room for improvement; they experience a ceiling effect [18, 28, 78]. With this model, 42% of the factors that explain a positive change in generic HRQoL were identified, resulting in a 58% of unknown variables or a black box. As reported in the review of Leijendekkers et al. [49], it is important to develop a core set of evaluation instruments to assess interventions for patients with lower limb amputation. The relatively large black box with unknown variables confirms the need for improving the currently used core set. Longitudinal studies regarding factors associated with change in generic HRQoL are lacking in bone-anchored prosthesis research and rare in socket-suspended prosthesis research [56]. The study of Migaou et al. [56] found that a higher walking ability, higher prosthetic use, lower age, lower psychical distress, higher functional status, more distal amputation level, and trauma as cause of amputation are associated with increased generic HRQoL. Several cross-sectional studies with patients using a socket-suspended prosthesis reported that more active social participation, better coping mechanisms, higher self-esteem, lower depression, less pain, positive employment status, and fewer comorbidities are associated with higher generic HRQoL [5, 23, 45, 74]. These factors may be part of the black box and may be used to optimize the core set for patients with a lower limb amputation. The association model for disease-specific HRQoL explained 77% of the

variance in change in disease-specific HRQoL in the study population.

Patients with dysvascular cause of amputation, lower prosthetic comfort combined with lower activity level, and lower prosthetic comfort combined with lower or higher activity level were more likely to experience a better disease-specific HRQoL. In addition, patients with an average mobility level were more likely to experience less improvement in disease-specific HRQoL. We interpret this as meaning that patients with a dysvascular amputation often cannot endure a prosthetic socket because of skin problems or reduced wound healing, which limits their mobility. Consequently, a bone-anchored prosthesis can offer more advantages to these patients compared with patients with other causes for amputation, thereby positively influencing disease-specific HRQoL [25]. The potential explanation for improvement in disease-specific HRQoL in patients with a higher mobility level (K4) is that these patients are often highly motivated and experience socket-related problems because of abundant use, all of which are resolved after bone-anchored prosthesis treatment. Patients with a lower mobility level (K0, not able to mobilize with a socket-suspended prosthesis) did not fill out the Q-TFA or the prosthetic comfort questionnaire at baseline and were therefore not included in the analysis. However, this group is likely to substantially improve in disease-specific HRQoL as the potential for progress in mobility is the largest. This can be confirmed by the decrease of patients without prosthetics over time (Fig. 1). This model explained 77% of the factors that are associated with a positive change in disease-specific HRQoL, leaving 23% unknown. Longitudinal studies on factors that are associated with change in disease-specific HRQoL are lacking in bone-anchored prosthesis and socket-suspended prosthesis research. Cross-sectional studies with patients using a socket-suspended prosthesis have reported that better coping mechanisms, higher self-esteem, absence of depression, good social support, fewer comorbidities, good participation in social activity, and good body perception are associated with higher disease-specific HRQoL [5, 45]. These factors may be part of the black box and may be used to optimize the core set for patients with a lower limb amputation [49].

Complications Within 24 Months

With regard to the occurrence of complications, the current study demonstrated that major complications are uncommon after bone-anchored prosthesis treatment at 24 months of follow-up. Minor complications such as soft tissue infections or stoma problems occurred most often; typically, these can be successfully treated nonoperatively in most patients. Patients treated with a tibial bone-

anchored prosthesis seem to have more infections compared with those with a femoral bone-anchored prosthesis; patients who undergo tibial bone-anchored prosthesis develop septic loosening more often, as reported by Atallah et al. [6]. This seems slightly paradoxical; patients treated at the tibial level logically experience fewer local stoma problems compared with those treated at the femoral level who have more soft tissue envelopes. This may be related to the learning curve, as surgeons have performed more bone-anchored prosthesis insertions in patients at the transfemoral level compared with the transtibial level. Furthermore, a substantial number of patients treated with two-stage surgery developed complications between surgical stages, mostly surgical site infections. In the current study, one individual died 8 months after a transfemoral amputation because of reasons unrelated to bone-anchored prosthesis treatment. No other deaths occurred. This is in line with the study of Hoellwarth et al. [40], who also reported that individuals who have undergone bone-anchored prosthesis treatment rarely die of problems related to the bone-anchored prosthesis. Instead, they generally die of unrelated causes.

Factors Associated With Minor to Severe Complications

The association model on minor complications explained 46% of the variance of minor complications occurring in the study population. Younger and higher functioning patients with a traumatic amputation had the lowest risk of minor complications, while women, older patients, patients with a lower activity level, and older patients with more time since amputation had the highest risk of minor complications. This higher risk of minor complications may be explained by older patients potentially having more comorbidities (such as worse general health) and poorer bone and soft tissues (including a longer time since primary amputation) [2]. In contrast, young active patients with trauma as the cause for amputation (who often do not have additional comorbidities) are at lowest risk for these minor complications. This model is based on both minor complications occurring between surgical stages (related to surgery) and minor complications occurring after surgical stage two (related to bone-anchored prosthesis use). The developed association model for moderate/severe complications explained 19% of the variance of moderate/severe complications occurring in the study population. Patients with a higher disease-specific HRQoL had the highest risk of moderate/severe complications. We do not have an explanation for the association between disease-specific HRQoL and moderate/severe events, but the low R^2 illustrated a large black box with unknown variables. As described in the studies of Hagberg et al. [34, 35], more active patients using a bone-anchored prosthesis have more

moderate/severe complications. In the current study, a real-life activity measure (for example, an accelerometer) was lacking. This may explain part of the large black box. However, only preoperative data were added to the association model. Therefore, a real-life activity measure using a bone-anchored prosthesis was not available because patients used a socket-suspended prosthesis preoperatively. In addition, Hagberg et al. [33, 35] used the OPRA implant system, which involved other prosthetic components than those used in our study. Therefore, the results from Hagberg et al. [33, 35] may not apply to our study population. Naturally, an association model (and the final decision tool) should be combined with the clinical view of healthcare professionals.

Conclusion

In agreement with earlier research, this study confirmed that physical generic HRQoL and disease-specific HRQoL improved after bone-anchored prosthesis use. Additionally, this study confirmed that a bone-anchored prosthesis results in relatively few major complications, and minor complications were often successfully treated with nonsurgical interventions. Patients who have a favorable risk-benefit ratio between improvements in HRQoL and potential treatment-related complications are most eligible for a bone-anchored prosthesis. These findings may be helpful to patients and treating physicians to aid in patient selection and to inform patients about potential short-term expectations of treatment. Future research should add more factors to the association models with the purpose of increasing the adjusted R^2 . Subsequently, current association models of generic HRQoL, disease-specific HRQoL, and complications must be validated in a new clinical setting, possibly yielding a prediction model and eventually a clinical decision rule.

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